

# Analysis of Variables Affecting Wound Healing After Musculoskeletal Sarcoma Resections

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Adjuvant treatment modalities, nutritional parameters, and allogeneic blood transfusions are investigated as possible contributing variables which may adversely affect wound healing after tumor resections for musculoskeletal sarcomas. Statistical analysis determined that preoperative chemotherapy, depressed preoperative hematocrit, and allogeneic blood transfusions (probably immunosuppression mediated) were the only significant factors affecting wound healing outcome. Suggestions to improve postoperative infection rates are discussed. © 1996 Wiley-Liss, Inc.

**KEY WORDS:** sarcoma, transfusions, nutrition, wound healing

## INTRODUCTION

The high rate of wound healing complications associated with musculoskeletal sarcoma resections is well documented. Wound complication rates ranging from 5% to 35% have been reported [1-11]. The actual rate of wound healing difficulties may in fact be higher than this. Clinical series often consist of select patient populations and only specific complications such as wound infections are documented. These studies have attempted to associate wound healing complications with a variety of parameters including chemotherapy, radiation therapy, the use of implants (allografts and/or endoprostheses), and extensive procedures with long operative times. We are unaware of any studies investigating the role of nutrition in wound healing following musculoskeletal sarcoma resections. Nutrition has demonstrated its positive role in wound healing and its negative influence on postoperative complications in orthopaedic surgery [12-19]. We hypothesized that poor preoperative nutrition would result in a higher wound complication rate.

Evidence for an immunosuppressive effect of allogeneic blood transfusion is difficult to refute. Clinical evidence is based on experiences in enhancing renal transplant graft survival as well as decreased survival following resections of breast/colon carcinomas and musculoskeletal sarcomas [20-25]. Allogeneic blood transfusion has been implicated as an independent risk factor for postoperative bacterial infections in patients undergoing abdominal [26-28], cardiac [29], vascular [30], orthopedic [31,32], or burn-related [33] surgery.

This study was undertaken to analyze which perioperative variables may be related to wound healing complications in patients undergoing resection of musculoskeletal sarcomas.

## MATERIALS AND METHODS

A retrospective review of all definitive musculoskeletal sarcoma resections performed by the senior author over a 62-month period was carried out. Inclusion criteria for this study were as follows: nonspinal soft tissue or skeletal sarcoma resections in skeletally mature individuals involving limb girdle amputation or limb salvage about the proximal humerus, hip, thigh, or knee. Staged procedures were excluded. All patients must have received their preoperative evaluation, surgery, and be followed postoperatively at our institution. Liberal use of parenteral perioperative antibiotics was routinely prescribed. In this group of patients, wound healing complications were defined as meeting at least one of the following criteria: operative revision of wound for dehiscence or hematoma; culture positive wound infection requiring irrigation, debridement, and antibiotic therapy; and wounds requiring daily dressing changes and healing by secondary intention.

In each patient, the hospital charts were reviewed. Demographic criteria such as patient age, gender, tumor

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**TABLE I. Individuals Not Meeting Inclusion Criteria**

Reason	N
Staged procedures	5
Skeletally immature	5
Sarcoma of distal upper or lower extremity	9
Amputation not involving limb girdles	8
Total	27

**TABLE II. Individuals Sustaining Wound-Healing Complications (N = 22)**

Reason	N
Dehiscence	10
Hematoma/seroma	3
Infection	9

**TABLE III. Restoration of Wound Healing Among 22 Individuals With Complications**

Procedure	N
Delayed primary closure	6
Secondary intention	8
Split thickness skin graft	4
Free tissue transfer	2
Total	20*

\*One patient underwent above-knee amputation, another underwent hip disarticulation. See text.

type, site and surgical procedure were identified. Adjuvant treatments including chemotherapy or external beam radiation therapy, the use of brachytherapy (intraoperative insertion of interstitial tissue implants in the tumor bed into which iridium 192 radiation pellets are placed), and the perioperative transfusion of allogeneic packed red blood cells were recorded. Finally, preoperative laboratory studies, including leukocyte cell count, total lymphocyte count, preoperative hematocrit, and serum albumin level, were recorded. These variables were analyzed comparing those individuals with wound healing complications to those without. Univariate (chi-square, categorical variables) and bivariate (Student's *t*-test two-tailed, unpaired, continuous variables) analyses were used for statistical comparisons.

## RESULTS

Eighty-seven patients met all the inclusion criteria for this study. Twenty-seven other patients did not meet the inclusion criteria and reasons for this are listed in Table I. Twenty-two patients (25.3%) sustained wound healing complications. All occurred within the first year. The remaining patients were each followed for a minimum of 24 months postoperatively, all with well-healed surgical wounds. Types of complications are given in Table II.

Ultimate healing was achieved in 20 of 22 cases by the means listed in Table III. Local healing was not achievable in two individuals: one patient underwent above-knee amputation, and another hip disarticulation. Both amputations were secondary to recurrent abscess following the initial limb salvage attempt. Complete data with the exception of total lymphocyte count ( $n = 49$ ) was available.

Table IV lists percentages of patients receiving each of the categorical variables affecting wound healing, as well as chi-square analysis of the data when comparing those with wound healing complications to those without. Table V lists the mean, standard error of the mean, and *P*-values for the continuous variables affecting wound healing when comparing the two groups. As can be seen from Tables IV and V, preoperative chemotherapy, decreased preoperative hematocrit, and receipt of large amounts of perioperative transfusions ( $>3$ ) were significantly ( $P < 0.05$ ) associated with wound healing complications.

## DISCUSSION

Wound-healing complications are anticipated in individuals undergoing musculoskeletal sarcoma resections. The procedures are lengthy and involve extensive exposures utilizing biologic and nonbiologic implants for reconstruction of the deficits. Furthermore, these patients frequently receive preoperative chemotherapy and/or radiation therapy and may be systemically ill on the basis of having a malignancy. Their nutritional status may be suboptimal. Thus, it would be of benefit to identify those variables which may influence wound healing in this population already at risk for wound healing complications in order to modulate them.

Nearly half of the wound healing complications (10/22) were from dehiscence of the surgical incision. Eight of these ten wounds opened while the sutures remained in place. Dermal sutures are typically removed between the second and fourth postoperative weeks. In retrospect, these wound breakdowns might have been avoided with the use of "prophylactic" local myocutaneous rotation flaps. Healthy tissue is needed to fill the large dead space resultant after extirpation of the neoplasm. Optimization of surgical techniques would have likely lowered the complication rate.

The importance of an individual's perioperative nutritional state in relation to postoperative outcome is well documented in the orthopaedic literature. Nutritional deficiencies have been discovered in orthopaedic surgical patients preoperatively [15] and have been associated with the impaired wound healing of amputations [12,34], increased complication rates in staged spine surgery [16], increased infection rates following single-stage spine surgery [19], increased mortality following hip fractures [13], and wound complications in total joint surgery [14]. With the above in mind, our results were unexpected.

**TABLE IV. Effect of Categorical Variables on Wound Healing Complications (Chi-Square Analysis)†**

	Allografts (%)	Chemotherapy (%)	XRT*	Brachytherapy (%)
Wound complications (N = 22)	4 (18.2)	9 (40.9)	5 (22.7)	1 (4.5)
No complications (N = 65)	17 (26.1)	12 (18.5)	9 (13.8)	10 (15.4)
X <sup>2</sup> *	0.57	4.52	0.96	1.75

†Some individuals are represented in more than one category, others did not receive any of the above adjuvant modalities.

\*XRT = Radiation therapy (range 3,500–4,500 cGy).

\*P < 0.05 occurs (1° freedom) when X<sup>2</sup> > 3.84.

**TABLE V. Effect of Continuous Variables on Wound Healing Complications (Unpaired, Two-Tailed Student's *t*-Test Analysis)\***

		Age (yr)	Albumin (g/dl)	WBC (×10 <sup>3</sup> )	TLC (cells/mm <sup>3</sup> ) × 1,000	Hct (%)	Transfusion (Units PRBC)
Wound complications	N	22	21	22	14	22	22
	Mean	55.1	3.99	6.0	1.16	37.7	5.18
	SEM	3.60	0.07	0.41	0.16	1.30	1.37
No complications	N	65	59	61	35	65	65
	Mean	48.5	4.01	6.90	1.20	40.6	2.46
	SEM	2.61	0.07	0.30	0.10	0.68	0.44
	P	0.19	0.82	0.11	0.84	0.04	0.01

\*N, number of patients for which data were available; SEM, standard error of the mean; WBC, white blood cell or leukocyte count; TLC, total lymphocyte count; Hct, preoperative hematocrit; PRBC, packed red blood cells.

The patients examined were adequately nourished based upon their albumin levels. A good nutritional status for wound healing has been previously defined as serum albumin levels  $\geq 3.5$  g/dl and a total lymphocyte count  $\geq 1,500$  cells/mm<sup>3</sup> [12,35]. Our patients had mean albumin levels  $> 3.5$  g/dl. The mean total lymphocyte counts in the two patient groups were  $< 15,000$ /mm<sup>3</sup> (1,160 and 1,200). It may be that in patients who are adequately nourished, or well nourished to an equal extent, other factors will be identified that affect wound healing, such as those identified in this study: preoperative chemotherapy, perioperative hematocrit, and perioperative blood transfusions.

Perioperative blood transfusions have been retrospectively associated with decreased 5-year survival rates in patients undergoing modified radical mastectomy for breast cancer, as well as colectomy for colon cancer [21,25,36,37]. Decreased survival rates have been associated with blood transfusions in patients undergoing amputations for nonmetastatic osteosarcoma [20]. Notably, in addition to the size of the primary tumor, the only other prognostic variable relative to survival and recurrence identified in a study of 156 patients treated for soft tissue sarcomas of the extremities was the receipt of blood transfusions [24].

An association between transfusions and postoperative wound infections has been reported for elective and trau-

matic abdominal surgery [26–28,38]. No such association has been previously identified for sarcomas. However, no support for a relationship between allogeneic blood transfusion and wound infection was demonstrated in a recent study involving total hip arthroplasty [39]. Most investigators have postulated that allogeneic blood transfusions may have an impact on the treatment of malignant tumors or on wound healing because of its effect in decreasing immunocompetence. This hypothesis stems largely from literature on renal transplants in which preoperative blood transfusions have resulted in enhanced graft survival [22,23]. Various alterations, largely involving cell-mediated immunosuppression, have been documented in individuals receiving allogeneic transfusions and have been postulated to have a role in the enhancement of graft survival [40–48].

Evidence suggests that the long-term presence of malignant cells alters the antigen receptors located on the surface of T cells [49]. While the initial work was performed on a murine model, preliminary results indicate T cells from human cancer patients have the same abnormality. The result is that malignant neoplasms are capable of depressing the immune system.

A recent report suggests that white blood cell filtered allogeneic blood transfusions may reduce the rate of postoperative colorectal surgery infection rates [50]. In this study population there are at least six variables that may

impede wound healing: premorbid nutritional status, complexity of reconstruction, extensiveness of surgical exposure, malignancy-specific induced immunosuppression, tumor site, or subpopulations of lymphoid cells.

The potential weaknesses of our study are that it was observational and not blinded or randomized. Therefore, the documented association between transfusion and infection cannot be taken as proof of a cause-and-effect relationship. Patients requiring more blood transfusions underwent longer and more extensive procedures and this alone may account for their greater incidence of wound healing complications. Blood loss alone, in the absence of allogeneic blood transfusion, has also been associated with decreased immunocompetence and increased rates of sepsis in an experimental model [51], and with anastomotic leak following esophagogastrectomy [52]. Ethical constraints do not, however, permit such a randomized clinical trial.

We hypothesize that allogeneic blood transfusions do have a role in depressing immunocompetence and therefore also wound healing potential. The association of preoperative chemotherapy as well as depressed preoperative hematocrit with wound healing complications can be accounted for by this mechanism as well. Patients receiving preoperative chemotherapy may have depressed marrow responsiveness and this decreased marrow activity is manifested in lower preoperative hematocrit values. In either case, the expected postoperative immune responsiveness is unable to occur due to a chemically and/or transfusion-mediated marrow suppression.

We determined that preoperative chemotherapy and blood transfusions ( $>3$  units) were significant variables associated with an adverse wound healing outcome. This finding has not before been published. As physicians hoping to find a variable that we could positively modulate, we were surprised to determine that nutrition did not negatively influence our study. It seems, however, that manipulation of the immune system and/or donor blood preparation holds promise to positively affect wound healing outcome.

In order to elucidate the role of allogeneic blood transfusions in wound healing, a prospective study comparing standard allogeneic blood transfusions to other modalities is required. These modalities may include autologous blood, leukocyte-poor filtered blood, or treatment with erythropoietin.

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